REMARKS

Applicant respectfully requests reconsideration of the application in view of the foregoing amendments, the following remarks, and the accompanying Rule 132 Declarations of Dr. Dana Hilt and Dr. Valerie Masini-Eteve.

I. Claim Amendments

Claim 15 is amended to conform to previous amendments to claim 5. Upon entry of the amendments, claims 1-3, 5-13, 15-21 and 23-28 will remain pending. These claims are presented for examination.

Applicant reserves the right to pursue any canceled subject matter in one or more applications with the same rights of priority as the instant application.

II. November 14, 2007 Office Interview

Applicant thanks Examiners Fetterolf and Helms for the courtesies extended to Applicant's representatives during the Office Interview conducted on November 14, 2007. As set forth in the Interview Summary, Applicant discussed the prior art rejections. The substance of the interview was that the prior art use of tamoxifen to reduce breast density does not render obvious the use of 4-hydroxy tamoxifen (4-OHT) to reduce breast density. Applicant also discussed the non-obviousness of compositions comprising 4-OHT and isopropyl myristate, as recited in the instant claims. These issues are discussed in more detail below.

III. The October 4, 2007 Office Action

The Office Action rejects the claims for alleged obviousness for the reasons set forth at pages 3-10 of the Office Action. The gist of the rejections is that it would have been obvious to use 4-OHT in place of tamoxifen to reduce breast density, and that the skilled artisan would have been motivated to make such a replacement and would have had a reasonable expectation of success in doing so. Applicant respectfully traverses.

A. *The Hilt Declaration Evidences Non-Obviousness*

The accompanying Rule 132 Declaration of Dr. Hilt explains and develops the issues discussed during the November 14, 2007, Office Interview, providing further evidence of the unpredictability in this field and demonstrating that it was not obvious to use 4-OHT to reduce breast density.

1. Tamoxifen is not a "pro-drug" of 4-OHT

At the outset, Dr. Hilt emphasizes that "it must be understood that tamoxifen is in no way a 'pro-drug' of 4-OHT." Hilt Declaration, ¶9. "Tamoxifen is metabolized into a number of different metabolites, several of which have been shown to be biologically active." Hilt Declaration, ¶9. Dr. Hilt's Declaration shows that, as currently understood, tamoxifen is metabolized into three primary metabolites, which are further metabolized into four secondary metabolites. Hilt Declaration, ¶9. 4-OHT is one of the three primary metabolites, and is not even the major primary metabolite. Instead, it is N-desmethyltamoxifen that is the major primary metabolite. Hilt Declaration, ¶9. N-desmethyltamoxifen is metabolized into three different secondary metabolites, only one of which also is a secondary metabolite of 4-OHT.

Another difference between tamoxifen and 4-OHT discussed by Dr. Hilt relates to estrogen receptor binding affinity. While "tamoxifen has about the same relative binding affinity for the alpha (7) and beta (6) estrogen receptors, 4-OHT has a higher relative binding affinity for the beta estrogen receptor (339) than the alpha estrogen receptor (178)." Hilt Declaration, ¶10. Thus, someone skilled in the art would not expect 4-OHT to be biologically equivalent to tamoxifen.

When the 4-OHT comprises a blend of *E* and *Z* isomers, as recited in claim 3, additional differences arise. As explained by Dr. Hilt, the commercially available form of tamoxifen is *trans (Z)* tamoxifen, which "metabolizes into the *Z* isomer of 4-OHT only." Hilt Declaration, ¶10. Dr. Hilt notes that if the relevant activity of tamoxifen were associated with only the *Z* isomer of 4-OHT—the only isomer formed *in vivo* from tamoxifen metabolization— then "administering a blend of *E* and *Z* isomers would be expected to result

in reduced efficacy, due to a smaller amount of active species being administered." Hilt Declaration, ¶10. This difference is significant because the *Z* and *E* isomers have different activities. The *Z* isomer of 4-OHT has anti-estrogenic activity, while the *E* isomer is a true selective estrogen receptor modulator (SERM) that exhibits both pro- and anti-estrogenic activity. Hilt Declaration, ¶10. Thus, as Dr. Hilt states, "administering a blend of the *Z* and *E* isomers of 4-OHT instead of tamoxifen may result in estrogenic activity where only anti-estrogenic activity is desired." Hilt Declaration, ¶10.

For at least these reasons, those skilled in the art understood at the time of the invention that administering 4-OHT would not be equivalent to administering tamoxifen.

2. SERM Activity Is Very Unpredictable

The obviousness rejections are based at least in part on the assumption that the known activity of 4-OHT, *e.g.*, its estrogen receptor binding activity, is predictive of usefulness in any therapy in which tamoxifen is useful, including the reduction of breast density. As Dr. Hilt explains in his declaration, SERM activity is not so predictable.

First, it must be recognized that "tamoxifen has many activities other than its anti-estrogen activity," as Dr. Hilt points out. Hilt Declaration, ¶12. For example, "[t]amoxifen can behave either as a frank estrogen (pure agonist), a partial agonist or as an antagonist, depending on the species, target organs, and end-points assessed." Hilt Declaration, ¶12 (quoting Lonning *et al.*, *Clin. Pharmacokinet.* 22: 327-58, 331 (1992) (copy attached to Hilt Declaration). Dr. Hilt also notes other proposed mechanisms of tamoxifen action that include "inhibit[ing] the conversion of estrone sulfate to estradiol, bind[ing] to 'antiestrogen binding sites,' and inhibit[ing] protein kinase C or calmodulin." *Id.*

Given the various activities of tamoxifen, it may not be surprising that "[d]ifferent tamoxifen metabolites have different activities." Hilt Declaration, ¶15. As noted in the Office Action, and confirmed in the literature cited by Dr. Hilt, "4-OHT has a strong binding affinity for the estrogen receptor and exhibits anti-estrogen activity *in vivo* in humans." Hilt Declaration, ¶15. "In contrast, dihydroxytamoxifen has an estrogen receptor binding affinity that is similar to estradiol, and is a 'partial agonist with anti-estrogenic properties' in a murine

uterine weight test, 'although both tamoxifen and dihydroxytamoxifen are full estrogen agonists in the mouse.'" Hilt Declaration, ¶15 (quoting Jordan *et al.*, *Breast Cancer Res. & Treat.* 2: 123-38, 131 (1982) (copy attached to Hilt Declaration). Another metabolite, Metabolite E, "appears to be a 'weak estrogen' in the immature rat uterine weight test, while Metabolite Y 'is a weak antiestrogen with partial estrogenic activity in the rat uterus.'" *Id.*

As explained by Dr. Hilt, "because tamoxifen has a number of biologic activities, and a number of biologically active metabolites, *a priori* predicting which specific activity and metabolite of tamoxifen might be useful for the treatment of any breast condition is not an undertaking that can be carried out with any reasonable level of certainty." Hilt Declaration, ¶13. Dr. Hilt attests that, prior to the work of Applicant, "it was not known that the anti-estrogen activity associated with . . . 4-OHT . . . is a relevant activity. . . for reducing breast density." Hilt Declaration, ¶12.

3. Anti-Estrogen Activity Does Not Predict Clinical Efficacy

While the Examiners have focused on the anti-estrogen activity of 4-OHT, Dr. Hilt explains "that anti-estrogen activity does not always correlate with pharmacological efficacy." Hilt Declaration, ¶19. Indeed, "an anti-estrogen agent that is effective for treating one condition may not be effective for treating another condition." Hilt Declaration, ¶19. Dr. Hilt discusses this point with reference to Gradishar & Jordan, *J. Clin. Oncol.* 15: 840-52 (1997) (copy attached to the Hilt Declaration). Those authors state plainly at page 841 that "[r]eceptor binding and biologic activity are now viewed as two separate functions."

As recounted by Dr. Hilt, "[t]he story of droloxifene taught those working in the field that estrogen receptor binding activity is not necessarily predictive of biological activity." Hilt Declaration, ¶20. "By 1994, this tamoxifen metabolite was proving to be a promising candidate for breast cancer therapy." Hilt Declaration, ¶20. "Droloxifene binds the estrogen receptor with 10-60 times the affinity of tamoxifen, and was found to be safer than tamoxifen in animal studies." Hilt Declaration, ¶20. Indeed, Gradishar & Jordan, *supra*, at page 841, characterized droloxifene as reflecting "[t]he principle of an antiestrogen with high affinity for the [estrogen receptor]."

The droloxifene story did not end well, however. As Dr. Hilt recounts, "by 1998, it was reported that 'interim data from a phase III trial was discouraging, showing that droloxifene offered no benefit beyond [tamoxifen].'" Hilt Declaration, ¶20 (quoting McNeil, *J. Nat'l Cancer Inst.* 90: 956-57, 957 (1998) (copy attached to Hilt Declaration) (internal quotations omitted). "In 2002, the investigators published the results of that trial, which was halted early, concluding that '[d]roloxifene was significantly less effective than tamoxifen overall.'" Hilt Declaration, ¶20 (quoting Buzdar *et al.*, *Breast Cancer Res. & Treat.* 73: 161-75, 161 (2002) (copy attached to Hilt Declaration). The whole droloxifine project was dropped. Hilt Declaration, ¶20.

Thus, by the time of the invention, those skilled in the art were aware that "identifying a high affinity anti-estrogenic metabolite of tamoxifen does not predict in any way utility, let alone a specific 'anti-estrogenic' clinically beneficial effect in a specific patient population." Hilt Declaration, ¶20. Thus, the skilled artisan could not have reasonably predicted from the known estrogen receptor binding activity of 4-OHT that 4-OHT could be used to reduce breast density.

Dr. Hilt discusses yet another example of the high level of unpredictability in this field—raloxifene. As explained by Dr. Hilt, "[r]aloxifene is a selective estrogen receptor modulator with anti-estrogen activity." Hilt Declaration, ¶21. Raloxifene "has a similar activity as tamoxifen in treating breast cancer in menopausal women, but is reported to have mixed effects on breast density." Hilt Declaration, ¶21. For example, Dr. Hilt cites Freedman *et al.*, *J. Nat'l Cancer Inst.* 93: 51-56 (2001) (copy attached to Hilt Declaration), as presenting data indicating that raloxifene "did not increase breast density," but achieved only a 1.5% or 1.7% (depending on the dose) decrease in breast density, where the placebo achieved a 1.3% decrease. On the other hand, Dr. Hilt cites Christodoulakos *et al.*, *Menopause* 9: 110-16 (2002) (abstract attached to Hilt Declaration), which reports on a study "where 6.3% of patients treated with raloxifene showed an increase in breast density, where no increase was seen in the control group." Hilt Declaration, ¶21. The story of raloxifene shows that even proven efficacy in one anti-estrogen context, *e.g.*, treatment of breast cancer, is not predictive of efficacy in another anti-estrogen context, *e.g.*, reduction of breast density.

Thus, as attested by Dr. Hilt, "those working in the field knew by 1998 (well before the patent applications were filed) that estrogen receptor binding activity was not necessarily predictive of clinical efficacy." Hilt Declaration, ¶22.

4. Other Active Metabolites of Tamoxifen Were Known

During the Office Interview, the Examiners asked whether the biological activity of other tamoxifen metabolites was known at the time of the invention. Dr. Hilt's Declaration discusses the state of the art with respect to tamoxifen metabolites, and provides evidence that other (perhaps more promising) metabolites were known in the art by the time of the invention.

As summarized by Dr. Hilt, "before the December 2002 priority date of the applications, a number of tamoxifen metabolites had been discovered and studied, several of which had raised interest as pharmacologically active metabolites that might be useful, for example, for treating breast cancer." Hilt Declaration, ¶14. For example, Dr. Hilt cites Jordan *et al.*, *Breast Cancer Res. & Treat.* 2: 123-38 (1982) (copy attached to Hilt Declaration), for providing a review of tamoxifen metabolites, including Metabolite A, Metabolite B (4-OHT), Metabolite D (catechol/dihydroxytamoxifen), Metabolite E, Metabolite F, Metabolite Y, N-desmethyl-tamoxifen and tamoxifen N-oxide. Hilt Declaration, ¶14. Dr. Hilt notes that "[m]any of these metabolites have significant anti-estrogen activities and inhibit estrogen signal transduction." Hilt Declaration, ¶14.

Dr. Hilt attests that "the multiplicity of biologic activities and active metabolites makes the prediction that 4-OHT would be either the optimal choice or even an obvious choice uncertain." Hilt Declaration, ¶14. To the contrary, Dr. Hilt notes that "endoxifen might have been considered to be the 'optimal' alternative to tamoxifen," Hilt Declaration, ¶17, for reasons explained in more detail below.

Endoxifen is also known as 4-hydroxy-N-desmethyltamoxifen. As noted by Dr. Hilt, "[b]y 1982, endoxifen had been discovered and reported to have an estrogen receptor binding affinity many times greater than tamoxifen." Hilt Declaration, ¶16. For example, Dr. Hilt cites data reported in Robertson *et al.*, *supra*, showing "endoxifen to have a relative binding

affinity for the rat uterine estrogen receptor of 143, as compared to a relative binding affinity of 2 for *trans (Z)* tamoxifen." Dr. Hilt recounts that, by 1990, it had been reported that "serum concentrations of endoxifen are generally higher than 4-OHT." Hilt Declaration, ¶17. By 1992, "endoxifen was being studied as having 'biological importance, with an affinity for the estrogen receptor several-fold higher than that of *trans*-tamoxifen.'" Hilt Declaration, ¶17 (quoting Lonning, *supra*, at 335). Indeed, endoxifen is still being studied as an important metabolite of tamoxifen in the treatment of breast cancer. *See, e.g.,* Jordan, *Steroids* 72: 829-42 (Abstract attached) ("Recent studies have identified . . . endoxifen as an important metabolite of tamoxifen necessary for antitumor actions.").

Accordingly, as attested by Dr. Hilt, "by the 2002 priority date of the applications, 4-OHT was not the only active metabolite of tamoxifen with promise for pharmacological activity and was not necessarily the most promising or viable choice for further study." Hilt Declaration, ¶18.

5. 4-OHT Efficacy Against Breast Density Was Not Predictable

In summary, Dr. Hilt's Declaration evidences that by 2002, "those working in the field knew that selective estrogen receptor modulators were highly unpredictable, can have different (even opposite) activities in different tissues, and can have different effects in pre- vs. post menopausal women." Hilt Declaration, ¶24. For at least these reasons, "it was not possible to predict from studies with tamoxifen, or from studies of 4-OHT in different patient populations, that 4-OHT could be used to . . . reduce breast density." Hilt Declaration, ¶24.

B. *The Recited Composition is Non-Obviousness*

The pending claims recite methods of reducing breast density using a pharmaceutical composition for percutaneous administration that comprises 4-OHT and isopropyl myristate. As discussed during the interview, this composition is non-obvious, because the ability of a particular penetration enhancer to be effective for a particular active agent in a particular formulation is unpredictable.

For example, Takahashi *et al.*, *Biol. Pharm. Bull.* 28: 870-75 (2005) (copy attached), reports that isopropyl myristate was not an effective penetration enhancer for a percutaneous composition comprising propofol as the active agent. As summarized in the "Discussion" at page 873, even though isopropyl myristate was "known to be a useful lipophilic solvent for transdermal absorption, . . . a significant enhancing effect was not observed after treatment with a mixture of [propofol] and [isopropyl myristate.]" This article evidences that, despite the theoretical usefulness of isopropyl myristate as a penetration enhancer, it did not prove useful in the specific composition at hand.

Of further interest is the authors' explanation of the poor enhancing effect of isopropyl myristate. In particular, they state that release of the propofol from the composition was suppressed because of the affinity between the propofol and the isopropyl myristate, which both are lipophilic. *See, e.g.,* Takahashi at 873-74. The active agent recited in the instant claims, 4-hydroxy tamoxifen, also is lipophilic. Thus, these teachings in Takahashi would discourage the skilled artisan from using a lipophilic penetration enhancer, such as isopropyl myristate, as a penetration enhancer for 4-hydroxy tamoxifen. This teaching away from the present invention further undermines the obviousness rejection.

Numerous other publications evidence the unpredictability of formulating effective percutaneous compositions, particularly with regard to the choice of penetration enhancer. For example, Sekine *et al.*, *Drug Design & Delivery* 1: 245-52 (1987) (copy attached), reports that azone was an effective absorption promoter for a transdermal hydroalcoholic gel composition comprising verapamil as the active agent, whereas isopropyl myristate was not. As reported in the Abstract, where azone increased plasma levels of verapamil by as much as ten-fold, isopropyl myristate had no effect on plasma levels, although it did appear to increase local transdermal absorption.

Lee *et al.*, Int'l J. Pharm. 33-39 (2006) (copy attached), reports that while isopropyl myristate was somewhat effective as a penetration enhancer for a percutaneous lidocaine composition, a combination of n-methyl pyrrolidone and isopropyl myristate enhanced drug flux 25 times greater than isopropyl myristate alone, and 4 times greater than n-methyl pyrrolidone alone.

Bergonzi *et al.*, Pharmazie 60: 36-38 (2005) (copy attached), assessed the effects of "[f]ive well-known penetration enhancers" on the permeation of sesquiterpenes, and reports that no sesquiterpene permeation was detected when isopropyl myristate was used as the enhancer. In contrast, oleic acid and dimethylsulfoxide were found to be effective penetration enhancers for sesquiterpenes. *See e.g.,* Bergonzi, page 37, Table 3.

These articles evidence that those skilled in the art would not consider the disclosure of the usefulness of a fatty acid ester as a penetration enhancer in one percutaneous composition to suggest that the same penetration enhancer would be useful in a different composition, comprising a different formulation or active agent. Thus, those skilled in the art would not understand from Ueda that isopropyl myristate would be an effective penetration enhancer for a percutaneous composition comprising 4-hydroxy tamoxifen, as claimed.

As further evidence of the unpredictability in this art, Applicant submits herewith a Declaration under 37 CFR § 1.132 by Valérie Masini-Etévé, Ph.D. As noted in the Declaration, Dr. Masini-Etévé is Head of Non Clinical R&D at Laboratoires Besins-International, the assignee of the captioned application. The results reported in Dr. Masini-Etévé's declaration demonstrate the unpredictability and performance variability associated with transdermal compositions in general, and with penetration enhancers in particular.

The data presented by Dr. Valérie Masini-Etévé show that two known penetration enhancers, oleic acid and isopropyl myristate, have unpredictable effects on permeation, depending, for example, on the active agent. As shown in the Declaration, oleic acid is not an effective penetration enhancer for 4-OHT, while isopropyl myristate is effective. Masini-Etévé Declaration, ¶ 4, 6, 17. Conversely, isopropyl myristate is not a particularly effective penetration enhancer for progesterone, while oleic acid is more effective. Masini-Etévé Declaration, ¶16, 17. As explained by Dr. Masini-Etévé, "[t]his unpredictability means that it is not possible to modify a given composition to replace the penetration enhancer with a different penetration enhancer, and reasonably predict that the modified composition will perform equivalently to the original composition. Masini-Etévé Declaration, ¶17. "Instead,

the suitability of a particular penetration enhancer must be determined experimentally for a given composition or active agent." Masini-Etévé Declaration, ¶17.

C. ***The Obviousness Rejections***

Applicant turns now to the specific rejections raised in the Action.

1. Claims 1-3, 5-13, 15-21, 24-25 and 27-28

Claims 1-3, 5-13, 15-21, 24-25 and 27-28 are rejected for alleged obviousness in view of (i) Atkinson *et al.*, *Cancer Epidem., Biomarkers & Prev. 863-66* (1999); (ii) Boyd *et al.*, *J. Nat'l Cancer Inst.* 87: 670-75 (1995); (iii) Kolb *et al.*, *Radiology* 225: 165-75 (2002); (iv) Mauvais-Jarvis *et al.*, U.S. Patent 4,919,937; (v) Mauvais-Jarvis *et al.*, *Cancer Res.* 46: 1521-25 (1986), and (vi) Ueda *et al.*, U.S. Patent 5,045,533. No combinations of these references renders obvious the present invention, however.

As set forth at pages 6-7 and 8-9 of the Action, the crux of the rejection is that "[i]t would have been *prima facie* obvious . . . to combine the teachings of the references so as to substitute oral tamoxifen administration . .. for percutaneous administration of 4-hydroxy tamoxifen," because "4-hydroxy tamoxifen is well known in the art to be the active form of tamoxifen at the molecular level, and, further overcomes the harmful side effects associated with oral . . . tamoxifen." While this statement may seem logical in hindsight, Dr. Hilt's Declaration evidences that, at the time of the invention, the replacement of tamoxifen with 4-OHT was neither an obvious choice nor a predictable undertaking. Instead, those skilled in the art understood that the clinical activity of selective estrogen receptor modulators (SERMs) such as 4-OHT was highly unpredictable and variable from tissue type to tissue type, patient population to patient population (particularly pre- versus post-menopausal patients), and condition to condition. Thus, prior to the present invention, the skilled artisan had no reasonable basis to expect that 4-OHT could be used successfully in place of tamoxifen to reduce breast density.

The only references cited for teaching any therapeutic use of 4-OHT are the Mauvais-Jarvis patent and Mauvais-Jarvis *Cancer Research* paper. These references do not support

obviousness, however, because they fail to provide any reasonable expectation of success. As explained by Dr. Hilt, although "[t]he Mauvais-Jarvis patent, at column 4, states that 'the drug described [4-OHT] finds application in the treatment of conditions of the breast, especially benign and even cancerous conditions of the breast,' that general statement does not provide a reasonable expectation of success in being able to use 4-OHT to treat the specific condition of breast density, e.g., to reduce breast density. Hilt Declaration, ¶30. Dr. Hilt reaches that conclusion because "[t]here is simply no data presented in the Mauvais-Jarvis patent indicating that 4-OHT would be effective to reduce breast density." Hilt Declaration, ¶30. The Mauvais-Jarvis *Cancer Research* paper similarly fails to support obviousness. As Dr. Hilt attests, "[t]his Mauvais-Jarvis reference reports on the tissue concentration and metabolism of *Z* 4-OHT after local administration to the breasts of female breast cancer patients, and does not present any data indicating that 4-OHT would be effective to reduce breast density." Hilt Declaration, ¶31. The lack of supporting data is particularly relevant in view of the high level of unpredictability in the field, as discussed above.

The Office Action sites Ueda (U.S. Patent 5,045,553) for teaching a percutaneous pharmaceutical composition comprising isopropyl myristate, but Ueda does not teach or suggest the composition recited in the instant claims. Ueda is directed to compositions for a dihydropyridine active agent. There is no teaching or suggestion in Ueda that its compositions might be useful for formulating other active agents for percutaneous delivery, let alone that they would be useful for formulating 4-OHT, as claimed. This omission is significant in view of the unpredictability in formulating effective percutaneous compositions, as discussed above and evidenced by the Masini-Etévé Declaration.

2. Claims 23 & 26

Claims 23 and 26 are rejected for alleged obviousness in view of Atkinson, Boyd, Kolb, the Mauvais-Jarvis patent, the Mauvais-Jarvis *Cancer Research* paper, Ueda, and Yamaguchi (U.S. Patent 5,829,877). This combination of references, however, fails to suggest the invention recited in claims 23 and 26, which are directed to embodiments where the administered pharmaceutical composition comprises 4-OHT, ethyl alcohol, isopropyl myristate, hydroxypropylcellulose and phosphate buffer.

The inability of Atkinson, Boyd, Kolb, the Mauvais-Jarvis patent, the Mauvais-Jarvis *Cancer Research* paper, and Ueda to teach the methods recited in independent claims 1 and 13 is demonstrated above. Yamaguchi is cited for allegedly teaching an alcoholic gel formulation comprising a phosphate buffer, ethyl alcohol, isopropyl myristate, and hydroxypropylcellulose. As pointed out in Applicant's previous response, however, Yamaguchi does not disclose any formulations comprising isopropyl myristate. While the Office Action cites column 11, lines 21-26, of Yamaguchi, the formulation reported in that example includes myristyl alcohol, not isopropyl myristate. The cited laundry lists of optional components (set forth at column 4, lines 38-42 of Yamaguchi) also do not mention isopropyl myristate. Moreover, Yamaguchi does not teach that its compositions are suitable for the percutaneous delivery of 4-OHT, as claimed. Thus, the obviousness rejection of claims 23 and 26 is improper, and should be withdrawn.

Conclusion

Applicant believes that the application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this application, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 4, 2008

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288